Expression of periostin according to endometrial cancer grade

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Abstract. While various molecular profiling methods have been described for the early diagnosis and prognostic process of endometrial cancer, the most common gynaecological cancer, the data obtained remain insufficient. The present study aimed to investigate the protein and gene expression of periostin and its role as a new biomarker in the diagnosis, treatment and prognosis of endometrial cancer. A total of 15 patients diagnosed with endometrial cancer at the Department of Pathology, Zeynep Kamil Training and Research Hospital (Istanbul, Turkey) and 15 patients who were operated on for non-tumour-related reasons, between December 2019 and May 2020, were included in the study. The cases diagnosed with endometrial cancer were divided into three groups: International Federation of Gynaecology and Obstetrics grades I, II and III. Pathology tumour blocks were selected for enzyme-linked immunosorbent assay and PCR studies in which periostin gene expression and protein levels were measured, respectively. A significant increase in periostin gene expression was observed in the endometrial cancer samples compared with that in the controls (3.40 ± 0.66 vs. 2.23 ± 0.47). The protein level of periostin in the tissues was found to be higher in the endometrial cancer samples than that in the control group (1.59 ± 0.31 vs. 0.94 ± 0.22). The levels of periostin protein and gene expression detected in the endometrial cancer samples increased as the grade increased. To the best of our knowledge, the current study is the first to determine the levels of periostin protein and gene expression in endometrial cancer. The results suggested that periostin may be used as a biomarker in the determination of higher histological grade in endometrial cancer.

Introduction

Endometrial cancer is the most common gynaecological cancer and is diagnosed in one out of 35 women in developed countries (1). When diagnosis of endometrial cancer is made, the first-line treatment is surgery, and then adjuvant treatment is recommended; however, adjuvant treatment is determined according to the tumour invasion depth, histological grade, patient age and lymph-vascular space invasion, which have an important role in the staging of endometrial cancer (2,3). While a high quality of life and improved clinical outcomes have recently been achieved for patients following use of chemotherapy and radiotherapy, the literature shows that 8% of patients with endometrial cancer in the high-risk group may develop distant metastases despite all treatment efforts (4,5). The early diagnosis of endometrial cancer will have a great impact on treatment management, the prognostic process and cost. While a number of molecular profiling studies indicate its value in the diagnosis and prognosis of endometrial cancer and its place in the risk classification of patients, the data available remain insufficient (6-9). This situation has driven researchers to seek novel biomarkers and target gene therapies.

Periostin (POSTN), a component of the extracellular matrix (ECM) produced by fibroblasts, interacts with integrin receptors and transmits signals to affect the cellular differentiation, adhesion and migration regulated by cytokines (10). The important role of POSTN in physiological processes has been demonstrated in a number of studies. For example, it has been shown that abnormal expression of POSTN is associated with the pathophysiology of asthma, myocardial damage and, most importantly, cancer (11-13). In cancer, POSTN interacts with integrin $\alpha v\beta 3$ in endothelial cells and activates the focal adhesion kinase pathway, resulting in tumour angiogenesis through vascular endothelial growth factor (VEGF) regulating receptor-2 (VEGFR-2) (14).

Hiroi *et al* (15) first discovered that the expression of POSTN in the human endometrium varies according to the menstrual cycle, and is regulated by the oestrogen and progesterone released from the ovary. The present study aimed to investigate the protein and gene expression of POSTN and its utility as a biomarker in the determination of higher histological grade in endometrial cancer.

Materials and methods

Patients. A total of 15 patients diagnosed with endometrial cancer and treated at the Department of Pathology Zeynep Kamil Training and Research Hospital (Istanbul, Turkey) and 15 patients who received surgery for non-tumour-related

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reasons between December 2019 and May 2020 were included in the present study. Three groups, International Federation of Gynaecology and Obstetrics grades I, II and III, were collected from the cases diagnosed with endometrial cancer via archive screening, with 5 patients in each group (16). All patients underwent a hysterectomy and bilateral salpingo-oophorectomy, as well as pelvic and/or paraaortic lymphadenectomy operations according to the pathology results obtained from frozen tissue samples. Tumour preparations of the cases from the pathology archive were re-evaluated, and endometrial cancer, non-tumour-related reason diagnosed blocks were selected for ELISA and PCR studies.

The control group consisted of patients who underwent a hysterectomy due to the indication of abnormal uterine bleeding; no cancer cells were detected in the endometrial sampling before the hysterectomy operation, and treatment-resistant bleeding continued.

Patients diagnosed with leiomyosarcoma, ovarian cancer and cervical cancer were excluded from the study.

Ethics. The present retrospective study was approved by the Ethics Committee of Zeynep Kamil Training and Research Hospital (Istanbul, Turkey; approval no. 116). All patients consented to treatment in accordance with institutional guidelines, and provided written informed consent at the time of the treatment. The present study was performed in accordance with the Declaration of Helsinki and the guidelines of the Ethics Committee of Zeynep Kamil Training and Research Hospital (Istanbul, Turkey).

Gene expression of POSTN by reverse transcription-quantitative (RT-q)PCR. From each paraffin block, five tissue sections (each 10-μm thick) were collected in 1.5-ml microfuge tubes. Extraction of total RNA from paraffin-embedded tissues was performed in duplicate using an FFPE RNA isolation kit (catalogue no. K156002; Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions. RNA (1 μg) was reverse transcribed to cDNA with the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions. The following primers were used: POSTN forward, 5'-TGCTCGAATCATCCATGGGAA-3' and reverse, 5'-TGTGTAAGCACACGGTCAATG-3'; and GAPDH forward, 5'-AGGGCTGCTTTTAACTCTGGT-3' and reverse 5'-CCCCACTTGATTTTGGAGGGA-3' (Merck KGaA). Amplification was performed with an ABI StepOnePlus detection system using SYBR Green PCR Master Mix (Applied Biosystems; Thermo Fisher Scientific, Inc.). The reaction conditions were as follows: 95˚C for 10 min, followed by 40 cycles of 95˚C for 15 sec and 60˚C for 1 min. The results were analysed using StepOne Software v2.3 (Applied Biosystems; Thermo Fisher Scientific, Inc.) and using the $2^{-\Delta\Delta Cq}$ method (17) and normalized to GAPDH mRNA. Data are expressed as fold-change relative to the control.

Protein levels of POSTN as determined by ELISA. A total of four formalin-fixed, paraffin-embedded tissue sections (each 10- to 15-μm thick) were placed in a 1.5 ml centrifuge tube. Samples were incubated with 250 μl buffer (pH 7.5; 0.05 M Tris, 1 mM EDTA and 0.5% Tween 20). The tube

was placed at 100˚C for 10 min and immediately placed into a dry ice ethanol slurry until frozen. Protein extraction of all samples was performed as previously described (18). Protein concentrations were measured using the Bradford method (19). POSTN levels were measured with the sandwich ELISA method following the kit manufacturer's instructions (cat. no. EH0255; Wuhan Fine Biotech Co., Ltd.) with an inter-assay coefficients of variability (cv) of <12% and an intra-assay cv of <10%, respectively. The mean minimum detectable quantity of human POSTN was 0.094 ng/ml. POSTN values are presented as ng/μg protein. All ELISA measurements were performed using a microplate reader (BioTek Instruments, Inc.).

Histopathological evaluation. Histopathological evaluation was performed on the samples of each of the 30 subjects. One sample per tumor centimeter was taken from each tumor and the samples were embedded in paraffin blocks and cut into 5-μm-thick sections using a Leica RM2125 RTS microtome device (Leica Microsystems GmbH). The selected paraffin sections were stained with haematoxylin and eosin (H/E) at room temperature for morphological evaluation (Figs. 1 and 2). One sample from each endometrial tumor was selected according to the WHO classification of tumors, 5th edition (16). A single sample was placed in each paraffin block. Proliferative endometrium samples were taken from hysterectomy materials that were surgically resected for reasons other than endometrial pathologies. All slides were examined under a light microscope (Olympus BX51; Olympus Corporation).

Statistical analysis. SPSS version 18.0 (SPSS, Inc.) was used for the statistical analysis. Values are expressed as the mean ± standard deviation for age, and as the mean ± standard error for the POSTN gene expression and protein levels. One-way ANOVA was used to analyse the differences among multiple groups, and an unpaired Student's t-test was used to compare data between two groups. Post-hoc tests analyses were performed using Tukey's test to compare the groups after one-way ANOVA, as the variances were homogeneous. Spearman's correlation analysis was used to analyse the correlations between cancer grade and POSTN protein levels and gene expression. P<0.05 was considered to indicate a statistically significant difference.

Results

The mean age was 55.6±9.0 years for the total patient cohort, with high similarity between the endometrial cancer and non-pathological control groups (58.8±8.8 vs. 52.4±8.3 years, respectively; P=0.05). H/E staining for endometrial cancer in Fig. 1; confluent glandular, cribriform pattern and intervening loss of stroma were observed. For proliferative endometrium (control) in Fig. 2; endometrial glands were observed to be uniform and widely spaced, and glandular epithelium consisted of low columnar cells.

To explore the role of POSTN in endometrial cancer tissues, the difference in expression was compared in the 15 endometrial cancer tissues and the 15 non-pathologically diagnosed hysterectomy tissues (control). Significantly increased POSTN gene expression was observed in cancer tissues compared with
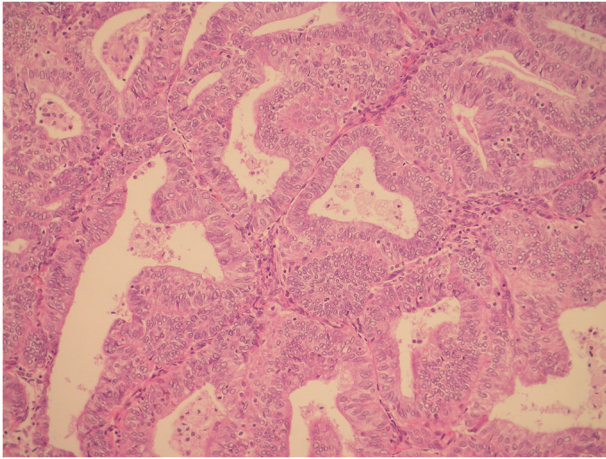
Figure 1. Haematoxylin and eosin-stained microscopic image of a patient diagnosed with endometrial cancer (magnification, x40).
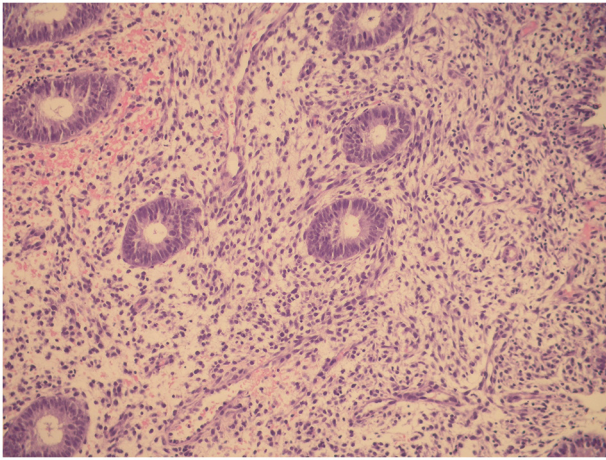

Figure 2. Haematoxylin and eosin-stained microscopic image of a patient from the control group (magnification, x40).

that in tissues without a pathological diagnosis (3.40±0.66 vs. 2.23±0.47, respectively) (Fig. 3A).

When the mean value for the protein level of POSTN was examined, it was found to be higher in endometrial cancer (1.59±0.31) compared with that in the control (0.94±0.22) (Fig. 3B).

Gene expression (P=0.005) and protein levels (P=0.003) were found to be significantly higher in the endometrial cancer group compared with those in the control group. Moreover, gene expression (P=0.007; Fig. 4A) and protein (P=0.015; Fig. 4B) levels were found to be significantly higher in the grade III patient group compared with those in the other grade groups and the control group. Grade I and II and the control groups were similar in terms of the mean gene expression and protein levels (P>0.05 for each).

In the results obtained in terms of demographic data, the median age in the endometrial cancer group was 57 years (range, 46-75 years) and the median age in the control group was 49 years (range, 43-67 years). The median age was 57 years (range, 53-75 years) in those with grade I disease, 52 years (range, 46-65 years) in those with grade II disease and 59 years (range, 50-73 years) in those with grade III disease.

The endometrial cancer grade was found to be significantly correlated with POSTN protein (P=0.003; Rho=0.719) and gene expression (P=0.010; Rho=0.643) levels (Fig. 5A and B).

Discussion

Epithelial-mesenchymal transition (EMT) is known as an important stage in cancer invasion and metastasis, and POSTN is a demonstrated factor in cell migration and transformation via EMT during cell differentiation and pathological progression (20). It has been shown that the effect of POSTN on EMT is mediated by the PI3K/AKT signalling pathway, which is regulated by cytokines, such as TGF-β1 (21,22). While POSTN is a marker of EMT, it is also an inducer of EMT (23). Previous studies have indicated that POSTN is expressed in large quantities in the tumour microenvironment and is one of the factors that mediate the communication between tumour cells and the ECM (21-23). The present study showed an increase in the protein level and gene expression of POSTN in endometrial cancer, and to the best of our knowledge, it is the first study reporting on this subject.

The endometrium consists of stromal and epithelial cells with eutopic and ectopic localization. In a previous study on the intrauterine physiological endometrium, POSTN expression was reported to increase significantly in the mid-proliferative and early secretory phases, while downregulated expression was observed in the late-proliferative, mid-secretory and late-secretory phases (15). The data obtained showed a strong association between oestrogen and progesterone supplementation and POSTN expression (15). POSTN expression is controlled by ovarian steroid hormones, and this may have a strong effect on physiological pregnancy and pathological processes (15). In other studies, POSTN was found to be overexpressed in tumour metastases, similar to certain mesenchymal cell markers, such as fibronectin and cadherin (24,25). POSTN interacts with integrin receptors to regulate the adhesion, differentiation and migration of undifferentiated cells with their characteristic fasciclin 1 domains (26). Cancer-associated fibroblasts are known as a major ECM component in the tumour microenvironment, and POSTN is partially produced by fibroblasts in metastatic lesions (27,28). In a previous study, it was determined that active fibroblasts secrete POSTN and support the differentiation, adhesion and migration of cholangiocarcinoma cells (29). Moreover, increased expression of POSTN has been shown to affect the tumour microenvironment by remodelling the ECM and interacting with integrins or other signalling molecules (10). The present study measured the protein level and gene expression of POSTN with regard to all three grades of endometrial cancer, and found that endometrial cancer grade was significantly correlated with gene expression and protein level, showing an increase in POSTN level as the grade increased. The present data support the results of previous studies indicating increased POSTN expression in malignant tissues such as colon, esophageal, nasopharyngeal carcinoma and pancreatic cancer (21-24).

In a large study conducted on patients diagnosed with ovarian cancer, POSTN was associated with drug resistance in epithelial ovarian cancer and gene expression profiling revealed a correlation between POSTN expression and chemotherapy resistance (30). In a previous study showing
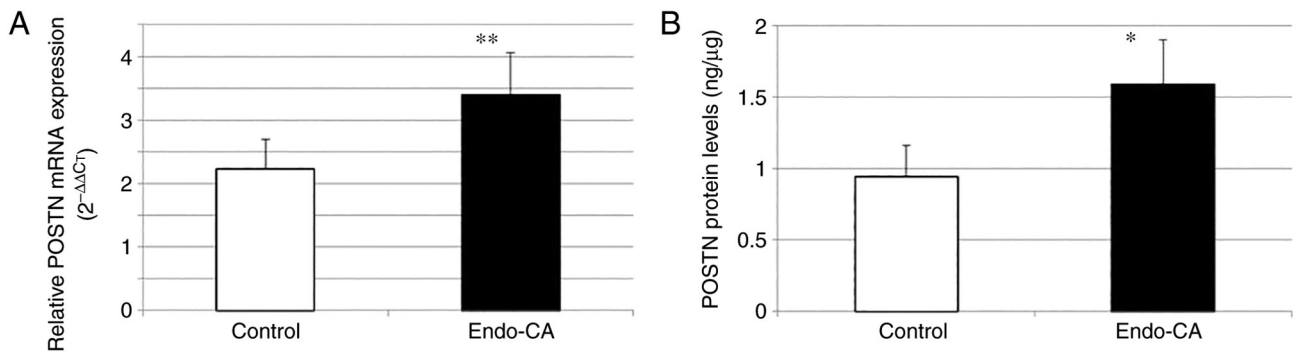
Figure 3. (A) Mean POSTN gene expression and (B) protein levels in the endometrial cancer patient and control groups. *P<0.05, **P<0.01 vs. control. Endo-CA, endometrial cancer; POSTN, periostin.
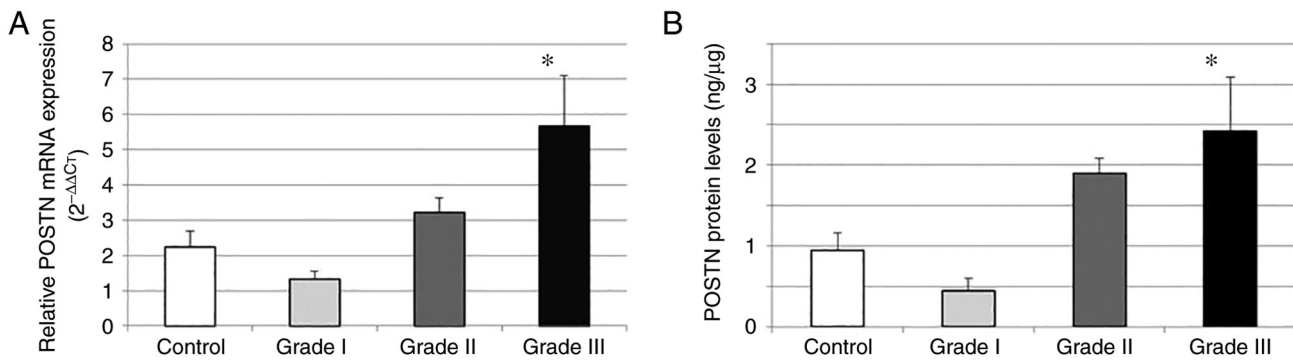

Figure 4. (A) Mean POSTN gene expression and (B) protein levels according to grade of endometrial cancer. *P<0.05 vs. control. POSTN, periostin.
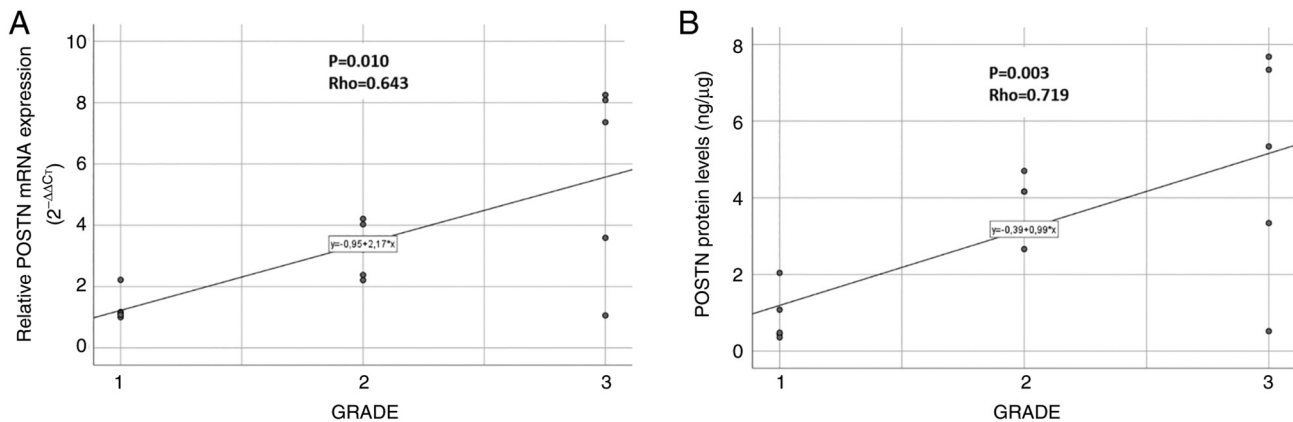

Figure 5. Scatterplots indicating the correlation between the grades and either (A) POSTN gene expression and (B) protein values. POSTN, periostin.

increased resistance to chemotherapy in chemosensitive ovarian cells under the influence of recombinant POSTN (31), it was reported that the proliferation and spread of non-small cell lung cancer cells could be inhibited, while sensitivity to chemotherapy was increased (32). In conclusion, targeting POSTN represents a novel therapeutic strategy for minimizing chemoresistance. There have been attempts to demonstrate the efficacy of targeting POSTN in the detection and treatment of tumours in several preclinical models. One of them used near-infrared fluorescence imaging with upper gastrointestinal endoscopy to detect preneoplastic lesions via optical imaging of POSTN (33). Kyutoku *et al* (34) reported that treatment with

PN1-Ab, an anti-POSTN antibody in breast cancer, was able to significantly inhibit the growth of primary tumours and the formation of lung metastases in an experimental study.

The present study has certain limitations. For example, patient serum samples were not assessed, as paraffin-embedded tissues were used. The aim of the study was to demonstrate the POSTN changes at the tissue level before proceeding with measuring changes in the serum in larger groups in future studies and the fact that the sample size was small was another limitation of the study.

The data obtained in the present study suggest that POSTN may be used as a biomarker in the early detection of

endometrial cancer and determination of higher histological grade. Further comprehensive studies are required to fully elucidate the clinical value and prognostic impact of POSTN.

Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

DH: Project development and manuscript writing, SG: Data management, data analysis and manuscript writing, EK: Data collection and management and data analysis, OC: Data analysis, manuscript writing and editing. DH and OC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the by the Ethics Committee of Zeynep Kamil Training and Research Hospital (Istanbul, Turkey; approval no. 116). All patients consented to treatment in accordance with institutional guidelines, and provided written informed consent at the time of the treatment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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